Differential arginine **dependence and the selective cytotoxic effects of activated macrophages for malignant cells in vitro.**

Currie G A; Basham C

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Normal and neoplastic cells from 4 species (man, rat, mouse and hamster) were examined for their dependence on exogenous L- **arginine** in tissue culture. The malignant cells **required** a higher concentration of L- **arginine** in the medium than their normal counterparts (with similar doubling times) to maintain optimal proliferation. Complete **arginine** deprivation resulted in equal growth inhibition of normal and malignant cells, but more rapid cytolysis of the malignant cell. Deprivation of L- **arginine** , followed 24 h later by rescue with L- **arginine** , allowed normal cells to proliferate, but the reproductive capacity of the malignant cells was irreversibly impaired. Since the cytotoxic activity of LPS-activated macrophages was associated with the release of arginase and was abrogated by excess L- **arginine** , it is suggested that the biological basis for the selective effects of such macrophages may reside in the L- **arginine** dependence of the target cells.

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Dec **1978** ,

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Descriptors: ***Arginine** --metabolism--ME; *Cytotoxicity, Immunologic --drug effects--DE; *Macrophages--immunology--IM; *Neoplasms, Experimental --immunology--IM; Animals; Arginase--metabolism--ME; **Arginine** --pharmacology--PD; **Cell** Count; **Cell** **Survival** --drug effects--DE; Cells, Cultured; Hamsters; Humans; Macrophages--enzymology--EN; Macrophages--metabolism--ME; Mice; Neoplasms...

Chemical Name: **Arginine** ; Arginase

7/3,K,AB/46 (Item 46 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

04256175 PMID: 4840563

Some biochemical considerations in utilization of n

Inhibition of nitric oxide **production in human subjects with hepatocellular carcinoma or metastatic melanoma by** arginine deiminase .

AUTHOR: Logan Theodore F (Reprint); Feun Lynn; Izzo Francesco; Ascierto Paulo; Ensor C Mark; Holtsberg Frederick W; Bomalaski John S; Clark Mike A; Curley Steven A
AUTHOR ADDRESS: Indiana University, Indianapolis, IN, USA**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 44 p1351 July 2003 2003
MEDIUM: print
CONFERENCE/MEETING: 94th Annual Meeting of the American Association for Cancer Research Washington, DC, USA July 11-14, 2003; 20030711
ISSN: 0197-016X
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

```
? s nitric(w)oxide
          307706  NITRIC
          903438  OXIDE
      S1  281477  NITRIC(W)OXIDE
? s argine(5n)(deficien? or depriv?)
             161  ARGINE
          700413  DEFICIEN?
          108117  DEPRIV?
      S2       0  ARGINE(5N)(DEFICIEN? OR DEPRIV?)
? s arginine
      S3  187312  ARGININE
? s s1 and s2
          281477  S1
               0  S2
      S4       0  S1 AND S2
? s nitric(5n)(synthase or synthetase)
          307706  NITRIC
          315377  SYNTHASE
           85044  SYNTHETASE
      S5  125840  NITRIC(5N)(SYNTHASE OR SYNTHETASE)
? s s1 and s3
          281477  S1
          187312  S3
      S6   68844  S1 AND S3
? s s5 and s6
          125840  S5
           68844  S6
      S7   41467  S5 AND S6
? s deiminase
      S8    1330  DEIMINASE
? s s7 and s8
           41467  S7
            1330  S8
      S9      48  S7 AND S8
? rd
>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
     S10      40  RD (unique items)
? t s10/3,k,ab/1-40

 10/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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15048241   PMID: 14599552
   Recombinant arginine deiminase as a differential modulator of
inducible (iNOS) and endothelial (eNOS) nitric oxide synthetase
 activity in cultured endothelial cells.
  Shen Li-Jiuan; Lin Wen-Chun; Beloussow Karin; Hosoya Ken-Ichi; Terasaki
Tetsuya; Ann David K; Shen Wei-Chiang
  Department of Pharmaceutical Sciences, School of Pharmacy, University of
Southern California, 1985 Zonal Avenue 404B, Los Angeles, CA 90089-9121,
USA.
  Biochemical pharmacology (England) Nov 15 2003, 66 (10) p1945-52,
ISSN 0006-2952 Journal Code: 0101032
  Contract/Grant No.: R01DE14183; DE; NIDCR
  Publishing Model Print
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  Languages: ENGLISH
```

Main Citation Owner: NLM
Record type: MEDLINE; Completed

Modulation of the extracellular level of **arginine** , substrate for **nitric oxide** synthetases, is a promising modality to alleviate certain pathological conditions where excess **nitric oxide** (NO) is produced. However, complications arise, as only preferential inhibition of the inducible **nitric oxide synthetase** (iNOS), but not endothelial **nitric oxide synthetase** (eNOS), is desired for the treatment of NO over-production. We investigated the effect of **arginine** deprivation mediated by a recombinant **arginine deiminase** (rADI) on the activity of iNOS and eNOS in an endothelial cell line, TR-BBB. Our results demonstrated that cytokine-induced NO production depends on the extracellular **arginine** as substrate. However, if sufficient citrulline is present in the medium, A23187-activated NO production by eNOS does not rely on extracellular **arginine** . Treatment with rADI can markedly inhibit cytokine-induced NO production via iNOS, but not A23187-activated NO production via eNOS. Our results also showed that the decrease of NO production by iNOS could be achieved by depleting **argini**

Recombinant arginine deiminase **inhibits** nitric oxide **production by inducible** nitric oxide synthetase **, but not endothelial** nitric oxide synthetase **, in cultured transgenic rat-blood brain barrier endothelial cells.**

AUTHOR: Shen Li-Jiuan Margarita (Reprint); Lin Wen Chun; Beloussow Karin Linda; Ann David; Shen Wei Chiang

AUTHOR ADDRESS: Pharmaceutical Sciences, University of Southern California, 1985 Zonal Ave., Los Angeles, CA, 90033, USA**USA
AUTHOR E-MAIL ADDRESS: shen@usc.edu; wenchunl@usc.edu; belousso@hsc.usc.edu ; ann@hsc.usc.edu; weishen@usc.edu
JOURNAL: FASEB Journal 17 (4-5): pAbstract No. 398.2 March 2003 2003
MEDIUM: e-file
CONFERENCE/MEETING: FASEB Meeting on Experimental Biology: Translating the Genome San Diego, CA, USA April 11-15, 2003; 20030411
SPONSOR: FASEB
ISSN: 0892-6638 _(ISSN print)
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English
ABSTRACT: **Arginine** , the substrate for **nitric oxide** synthetases (NOS), is a target in pathological conditions of the cardiovascular system where excess NO is produced. However, complications arise, as only selective inhibition of the iNOS is desired and not of eNOS. We investigated the effect of a recombinant **arginine deiminase** (rADI) on **arginine** deprivation, iNOS and eNOS in transgenic rat blood brain barrier endothealial cells. Our results demonstrated that cytokine-induced NO production depends on the extracellular **arginine** as substrate. However, if sufficient citrulline is present in the medium, A23187-activated NO production by eNOS does not rely on extracellular **arginine** . The effect of rADI can significantly inhibit cyokine-induced NO production ($p<0.001$), but not A23187-activated NO production. Thus, rADI appears to be a selective iNOS inhibitor. This is possibly due to the co-localization of eNOS and the **arginine** regeneration enzymes. Our results also showed that the expression of three **arginine** -related proteins, iNOS, argininosuccinate synthetase and **arginine** transporter(s), were up regulated by rADI. Therefore, a decrease of NO production by iNOS in endothelial cells could be achieved by depleting **arginine** from the medium even under the conditions that would up-regulate iNOS expression. An understanding of rADI-mediated regulation of gene expression can be crucial for treatment of NO over-production.
Recombinant arginine deiminase **inhibits** nitric oxide **production by inducible** nitric oxide synthetase **, but not endothelial** nitric oxide synthetase **, in cultured transgenic rat-blood brain barrier endothelial cells.**

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411304 Genuine Article#: TB468 Number of References: 21
Title: MACROPHAGE ACTIVATION BY CULTURE IN AN ANOXIC ENVIRONMENT (Abstract Available)
Author(s): ALBINA JE; HENRY WL; MASTROFRANCESCO B; MARTIN BA; REICHNER JS
Corporate Source: RHODE ISL HOSP,DEPT SURG,DIV SURG RES,593 EDDY ST/PROVIDENCE//RI/02903; BROWN UNIV,SCH MED/PROVIDENCE//RI/02903
Journal: JOURNAL OF IMMUNOLOGY, 1995, V155, N9 (NOV 1), P4391-4396
ISSN: 0022-1767
Language: ENGLISH Document Type: ARTICLE
Abstract: The extracellular amino acid composition of experimental wounds in rats during peak macrophage infiltration bears the imprint of the elevated arginase activity present in wound fluid: L- **arginine** is found in this space in concentrations markedly lower, and L-ornithine in concentrations markedly higher, than those that are detectable in plasma. No evidence, in the form of L-citrulline or NO2- accumulation, can be found at this time for **nitric oxide synthase** (NOS) activity. Wound-derived macrophages, however, metabolize L- **arginine** through both arginase and NOS in culture. Given the requirements of NOS for O-2 and the reduced O-2 tension in wounds, experiments were performed to determine the role of O-2 availability on the metabolism of L- **arginine** by wound-derived macrophages. Results demonstrated that, beyond inhibiting NOS, culture of wound-derived macrophages in an anoxic environment provided an activation signal, markedly increasing total l.- **arginine** metabolism, arginase activity, NOS protein content, and the release of TNF-alpha and IL-6. Neither resident nor Corynebacterium parvum-elicited peritoneal macrophages responded to anoxic culture with increases in L- **arginine** utilization, arginase activity or, in the case of resident macrophages, in NOS protein content. The enhanced TNF-alpha and IL-6 release induced by anoxia in wound-derived macrophages was also found in resident peritoneal macrophages. Anoxia appears to act, then, as an inducer of activation-associated traits in macrophages obtained from different sites.

...Abstract: macrophage infiltration bears the imprint of the elevated arginase activity present in wound fluid: L- **arginine** is found in this space in concentrations markedly lower, and L-ornithine in concentrations markedly...

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haracterization of Mycoplasma arginine deiminase **expressed in E. coli and its inhibitory regulation of** nitric oxide **synthesis**

AUTHOR: Noh Eun Joo; Kang Sang Wook; Shin Yong Jae; Kim Dong Chung; Park In Sun; Kim Min Young; Chun Boe Gwun; Min Bon Hong (Reprint)
AUTHOR ADDRESS: Department of Pharmacology, College of Medicine, Korea University, Seoul, 136-705, South Korea**South Korea
JOURNAL: Molecules and Cells 13 (1): p137-143 February 28, 2002 2002
MEDIUM: print
ISSN: 1016-8478
DOCUMENT TYPE: Article
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ABSTRACT: We previously reported that a cytostatic protein that is found in ASC-17D Sertoli cell-conditioned media was Mycoplasma **arginine deiminase** (ADI), which hydrolyzes L- **arginine** into L-citrulline and ammonia. Here, we report the over-expression of recombinant ADI (rADI) in E. coli and the down-regulation of lipopolysaccharide (LPS) induced- **nitric oxide** (NO) production by rADI treatment. We cloned the ADI gene from Mycoplasma arginini genomic DNA by a polymerase chain reaction, and changed five TGA tryptophan codons (stop codon in E. coli) to TGG codons in the coding region by site-directed mutagenesis in order to express in E. coli. The rADI was purified to apparent homogeneity by DEAE-Sepharose and **arginine** -affinity chromatography. The rADI expressed in E. coli was identified as 45 kDa on SDS-PAGE and 90 kDa on native PAGE, implying that it exists as a dimer like ADI of M. arginini. The Km for **arginine** of rADI was approximately 370+-50 muM. Its optimal temperature and pH were 41degreeC and pH 6.4, respectively, and enzyme activity remained gtoreq50% for 5 d at physiological temperature and pH. Treatment of purified rADI suppressed NO production in macrophage-like RAW 264.7 and primary glial cells that were exposed to LPS. Furthermore, an intraperitoneal injection of rADI significantly suppressed the rise of blood nitrite/nitrate levels that were induced by the systemic administration of bacterial endotoxin LPS to mice, resulting in an improvement in their survival rate. These results suggest that the depletion of blood **arginine** with an **arginine** -metabolizing enzyme, such as ADI, could suppress excessive production of NO that is caused by inducible NOS (iNOS) during the endotoxemia. Also, rADI may be used as a new approach to control NO-related diseases, such as sepsis.

Characterization of Mycoplasma arginine deiminase **expressed in E. coli and its inhibitory regulation of** nitric oxide **synthesis**

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